CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40263

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #40-263
SPONSOR: Bigmar, Inc.
DRUG: Methotrexate Sodium
DOSAGE FORM: Injection
STRENGTH: 25 mg/mL (Preserved)
REFERENCE PRODUCT: Lederle's Methotrexate Sodium Injection, USP, 25 mg/mL.
SUBMISSION TYPE: Waiver

STUDY SUMMARY: Not Applicable

DISSOLUTION: Not Applicable

WAIVER SUMMARY: The waiver of the *in vivo* bioequivalence study for the test product, Methotrexate Sodium Injection, USP, 25 mg/mL is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product formulation to be bioequivalent to the reference drug Lederle's Methotrexate Sodium Injection, USP, 25 mg/mL.

PRIMARY REVIEWER: Zakaria Z.Wahba, Ph.D. BRANCH: III

INITIAL: ZZW DATE: 2/23/98

GROUP LEADER: Moheb H. Makary, Ph.D. BRANCH: III

INITIAL: MHM DATE: 2/23/98

DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: DPC DATE: 2/23/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: _____ DATE: _____

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BIOEQUIVALENCY COMMENTS

ANDA: #40-263 APPLICANT: Bigmar, Inc.

DRUG PRODUCT: Methotrexate Sodium Injection (Preserved), USP, 25 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 40-263
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Nerurkar for BioSign Off List
HFD-658/ Z. Wahba
BIO DRUG FILE /S/

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BIOEQUIVALENCY - ACCEPTABLE

1. **WAIVER** (WAI) Strengths: 25mg/mL Inj.(Perserved)

Outcome: AC

OUTCOME DECISIONS:

AC - Acceptable

WINBIO COMMENTS:

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ 12/12/97

Concur: /S/ Date: 12/31/97
Dale P. Conner, Pharm.D.
Acting Director
Division of Bioequivalence

Methotrexate Sodium Injection, USP
25 mg/mL (**Preserved**)
ANDA # **40-263**
Reviewer: Z.Z. Wahba
File #40263a.298

Bigmar, Inc.
Johnstown, OH
Submission Date:
November 21, 1997

AN AMENDMENT TO A REVIEWED WAIVER REQUEST (DATED 12/31/1997)

BACKGROUND

1. On July 28, 1997, the firm requested a waiver of in vivo bioequivalence study requirements for its drug product, Methotrexate Sodium Injection, USP, 25 mg/mL. The reference listed drug (RLD) is Methotrexate Sodium Injection, USP, 25 mg/mL (Lederle, NDA #11719). The waiver request for the firm's test product was granted on 12/31/1997 based on 21 CFR Section 320.22(b)(1) of Bioavailability/Bioequivalence Regulations.

2. In this application the firm has submitted a supplement requesting approval to change the concentration of the inactive ingredient, sodium chloride from mg/mL to mg. This change will make the firm's test product exactly identical to the reference listed product.

FORMULATION COMPARISON

Comparative compositions of the test and the reference products are as follows:

Comparison of Formulation

Ingredient	Test Product (mg/mL)	RLD (mg/mL)
Methotrexate, USP	25.00	25.00
Benzyl Alcohol	(0.90% W/V)	0.90% W/V
Sodium Chloride	(0.26% W/V)	0.26% W/V
Sodium Hydroxide and/or Hydrochloric Acid	Adjust pH ?	Adjust pH (approximately 8.5)
Sterile Water for Injection	qs to 100%	qs to 100%

* Methotrexate Sodium Injection (Preserved), Isotonic Liquid, available in 25 mg/mL, 2 mL (50 mg) and 10 mL (250 mg) vials.

COMMENTS

1. The drug product is classified "AP" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".

2. The test drug product contains the same active and inactive ingredients in the same concentration and dosage form as the currently approved listed reference product.

3. The waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Bigmar Inc. demonstrates that Methotrexate Sodium Injection (Preserved), USP, 25 mg/mL, falls under 21 CFR Section 320.22(b)(1) of Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for Methotrexate Sodium Injection, USP, 25 mg/mL, of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Bigmar's Methotrexate Sodium Injection (Preserved), USP, 25 mg/mL to be bioequivalent to the reference listed product, Lederle's Methotrexate Sodium Injection (Preserved), USP, 25 mg/mL.

The firm should be informed of the recommendation.

BIOEQUIVALENCY COMMENTS

ANDA: #40-263 APPLICANT: Bigmar, Inc.

DRUG PRODUCT: Methotrexate Sodium Injection (Preserved), USP, 25 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Methotrexate Sodium Injection, USP
25 mg/mL (**Preserved**)
ANDA # **40-263**
Reviewer: Z.Z. Wahba
File #40263w.797

Bigmar, Inc.
Johnstown, OH
Submission Date:
July 28, 1997

REVIEW OF A WAIVER REQUEST

BACKGROUND

1. The firm has requested a waiver of in vivo bioequivalence study requirements for its drug product, Methotrexate Sodium Injection, USP, 25 mg/mL. The reference listed drug (RLD) is Methotrexate Sodium Injection, USP, 25 mg/mL (Lederle, NDA #11719).

2. The drug is indicated for the of neoplastic diseases (excluding meningeal leukemia, high dose methotrexate therapy, or intrathecal use) and severe psoriasis.

FORMULATION COMPARISON

Comparative compositions of the test and the reference products are as follows:

Comparison of Formulation

Ingredient	Test Product (mg/mL)	RLD (mg/mL)
Methotrexate, USP	25.00	25.00
Benzyl Alcohol	0.90% W/V	0.90% W/V
Sodium Chloride		0.26% W/V
Sterile Water for Injection	qs ad 100%	qs ad 100%
Sodium Hydroxide and/or Hydrochloric Acid	Adjust pH	Adjust pH (approximately 8.5)

* Methotrexate Sodium Injection (Preserved), Isotonic Liquid, available in 25 mg/mL, 2 mL (50 mg) and 10 mL (250 mg) vials.

COMMENTS

1. The drug product is classified "AP" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".

2. The test drug product contains the same active ingredient in the same strength and dosage form as the currently approved listed reference product.

3. The concentration that is provided in the statement of chemical composition for sodium chloride fall in the acceptable range of the Agency's Inactive Ingredient Guide.

4. The waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Bigmar Inc. demonstrates that Methotrexate Sodium Injection (Preserved), USP, 25 mg/mL, falls under 21 CFR Section 320.22(b)(1) of Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for Methotrexate Sodium Injection, USP, 25 mg/mL, of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Bigmar's Methotrexate Sodium Injection (Preserved), USP, 25 mg/mL to be bioequivalent to the reference listed product, Lederle's Methotrexate Sodium Injection (Preserved), USP, 25 mg/mL.

The firm should be informed of the recommendation.